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SYNTHESES OF NITRILE AND METHYL ESTER CORRESPONDING TO (dl)-SARKOMYCIN AND OF RELATED COMPOUNDS.

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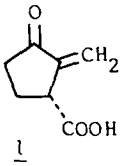
Abstract. Nitrile 6a and ester 12 corresponding to (dl)-sarkomycin, 6- and 7-membered rings analogue nitriles 6b, 6c, and 3-methyl substituted nitrile 6d were prepared. Conjugate addition of cyanotrimethyl silane to cyclic α-enones gave 3-trimethylsiloxy 2-cycloalkene carbonitriles. Their alkylation with chloromethyl phenyl sulfide followed by oxone oxidation to sulfones and sulfinic acid elimination on basic alumina led to α-methylene carbonyl compounds. Obtention of the ester 12 involved acetalization of 3-oxo 2-phenylthiomethyl cyclopentane carbonitrile, basic hydrolysis into acid, deacetalization, esterification, oxidation and elimination of sulfinic acid.



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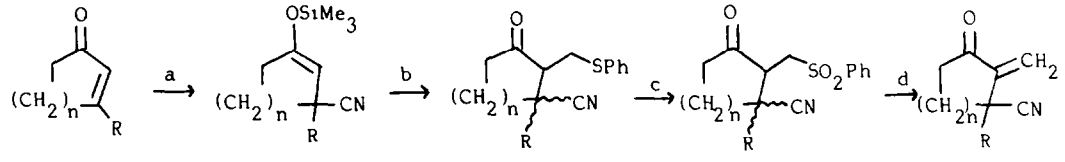
Several syntheses of the antitumor sarkomycin 1 and of some related compounds, ester and nitrile, have been reported. Most publications in this area have appeared very recently [1]. In spite of the interest of these sequencies which are elegant, most of them employ either not easily available materials and/or complicated experimental procedures. Thus, these preparations do not seem to be convenient for the obtention of several hundred milligrams of pure products. These difficulties which have already been pointed out [1j] led to a new synthesis of methyl ester corresponding to sarkomycin[2]. We have approached this problem [3] with the aim of preparing not only this last product but also nitriles and esters with different ring sizes in order to examine if there is any relationship between structure and biological activity. Therefore we needed short and adequate ways for the preparation of sufficient amounts of these sensitive compounds in a good purity state.

We firstly obtained the nitrile corresponding to (dl)-sarkomycin 6a by a four step sequence (scheme I). The conjugate addition of cyanotrimethyl silane in the presence of triethylaluminium [3] to cyclopentenone in hexane solution [3] gave the silylenol ether 3a which was very sensitive to hydrolysis. However its purification was made possible without acidic treatment or extraction, via decomposition of the excess cyanotrimethyl silane and triethylaluminium by addition of the strict amount of required water. Alkylation of silylenol ether 3a by chloromethyl phenyl sulfide in the presence of zinc bromide [5] gave 4a in 35% yield from 2a. Oxidation of 4a with oxone [6] led to the expected sulfone 5a but the elimination



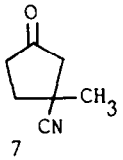
2a R = H ; n = 1	3a-d	4a Yield[e] 35%	5a-d	6a Yield[f] 54%
b R = H ; n = 2		b 46%		b 20%
c R = H ; n = 3		c 38%		c 45%
d R = Me ; n = 1		d 25%		d 58%

(a) CNSiMe3, Et3Al ; (b) PhSCH2Cl, ZnBr2(TiCl4 for 3d) ; (c) Oxone (2KHSO5, KHSO4, K2SO4) ; (d) basic Al2O3 (-PhSO2H) ; (e) yield in isolated product from 2a-d ; (f) yield in isolated product from 4a-d (except for 6b which was not obtained in a pure state).

Scheme 1

of sulfinic acid to give nitrile 6a by usual methods gave disappointing results. For instance the treatment of this sulfone 5a with 1,8 diazabicyclo[5,4,0]7-undecene (DBU) (1 equivalent) in dichloromethane (20°C) only gave the isomerization product (2-methyl 3-oxo 1-cyclopentanecarbonitrile) and the treatment with potassium carbonate in tetrahydrofuran (20°C) gave 6a very slowly, but this product was not stable in these conditions and it could not be obtained in reasonable yield. Fortunately we discovered this transformation to be possible on basic alumina in methylene chloride. This mild method led to the nitrile 6a in high crude yield from the sulfide 4a (after the isolation by column chromatography, the yield was 54%). This sequence is shorter than the previously reported one[1c] and gives a better overall yield. On the other hand oxidation of the sulfide 4a to the corresponding sulfoxide with sodium periodate followed either by a treatment with silicagel [7] or by reflux in chloroform gave impure 6a in a lower yield.

We also obtained 6- and 7-membered rings analogues 6b, 6c and 3-methyl substituted nitrile 6d (scheme I). The preparations of 6b and 6c from 2b and 2c were similar to the one used for 6a. In the case of 6d, both isomers of the intermediate 4d were obtained in 21% yield only when $ZnBr_2$ was used as catalyst in the alkylation step. The use of $TiCl_4$ led to a slight improvement (25%). This low yield is mainly due to the additional formation of the corresponding ketone 7, in a higher proportion than in the other cases (a,b,c) (4d/7 = 0.6). The methyl group in the 3-position probably reduces the rate of alkylation thus enhancing the amount of the unalkylated ketone. We tried to improve the method via formation of the more hindered silylenol ether 8 which was obtained by conjugate addition of cyanodimethyltertiobutyl silane to 3-methylcyclopentenone in the presence of triethylaluminium ; however no increase in yield was obtained.



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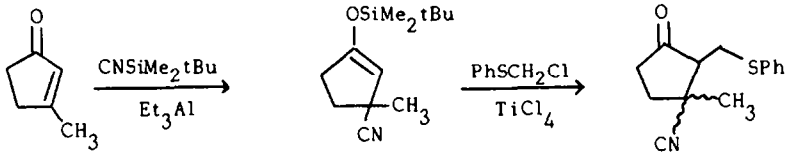
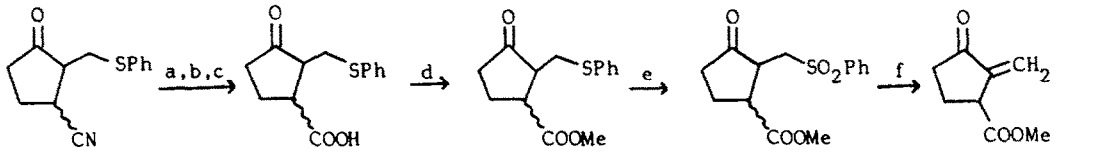


2d 8 4d

The least stable of compounds 6a-d is 6b which could not be obtained in a pure state. The low yield of the conversion 4b ⟶ 6b (estimated by NMR) is due to this unstability. The three other ones, 6a and 6c-d polymerize quickly at room temperature when neat but they can be stored several months in an organic solvent at -20°C, as checked by spectroscopic methods.

The methyl ester 12 corresponding to sarkomycin was prepared from 4a (scheme 2). Protection of the carbonyl group followed by basic hydrolysis and deacetalization gave acid 9 in 68% yield.



4a 9 (68%)[g] 10 (100%)[g] 11 12 (52% from 10)[g]

(a) $HOCH_2CH_2OH$, p-TsOH ; (b) KOH, H_2O, $HOCH_2CH_2OH$, 120°C ; (c) Me_2CO, H_2SO_4 ; (d) CH_2N_2 ; (e) oxone ($2KHSO_5$, $KHSO_4$, K_2SO_4) ; (f) basic Al_2O_3 (-$PhSO_2H$) ; (g) yield in isolated product.

Scheme 2

Esterification of 9 followed by oxidation led to sulfone 11. Elimination of sulfinic acid with basic alumina gave the expected product 12 in 52% yield. On the other hand the yield was lower via treatment with silicagel of the sulfoxide corresponding to 10 [7], a result analogous to the previously described one in the obtention of 6a (see above).

These preparations which need only easily available materials and rather simple experimental conditions are described in the experimental section starting from 0.02 mole of cyclenone, but in several experiments the key intermediates 4 were prepared in a larger scale [10]. Compounds 4 were obtained in two steps only from α-enones and it was not necessary to isolate the intermediate silylenol ether 3. Finally our methods are efficient for obtention of appreciable amounts of practically pure products (6 and 12) ; the exocyclic position of the sulfone group induces a single regioisomer elimination product provided that, in mild conditions, no isomerization of the double bond takes place. Furthermore our new sequence to prepare the nitrile corresponding to sarkomycin is indubitably more convenient than the previously reported one [1c] as it avoids the use of 2-(carbomethoxy) cyclopent-2-enone, a not easily available reagent which polymerizes readily when neat. Moreover it gives a better overall yield in four steps only. On the other hand, although the methyl ester could be efficiently obtained by other ways [1], ours is interesting when taking into account its simplicity. It is also important to note that here we describe the first method which gives, by the same pathways, several products with different ring sizes. Another advantage of our work is that some of the intermediate compounds may be interesting for the biological research which is in progress.

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Experimental Section

Proton NMR spectra were obtained on either a Perkin-Elmer R 12A (60 MHz) or a Perkin-Elmer R 32 (90 MHz) instrument and carbon NMR spectra on a Bruker AM 250 instrument. Mass spectra were recorded on a Girdel-Nermag R 10-10 or a GC/MS Hewlett-Packard 5992A mass spectrometer. High resolution mass spectra were measured on a Kratos MS 80 RF mass spectrometer by the peak matching method 8. IR spectra were determined on a Perkin-Elmer 682. UV spectra were recorded on a Kontron Uvikon 810. Microanalyses were performed by the service de micronalyse CNRS ICSN Gif sur Yvette. The preparative column chromatographies were run on silica gel Merck 60 (0.063 - 0.200 mm).

General procedure for cyanotrimethyl silane conjugate addition to cyclenones for preparation of silylenol ethers 3a-d

To a stirred solution of 2.73 g (24 mmol) of triethylaluminium in 35 mL of hexane at 20°C under nitrogen, 4.36 g (44 mmol) of cyanotrimethyl silane 9 was added. A solution of 20 mmol 10 of cyclenone in 80 mL of hexane was then added in 20 min and the mixture was heated to 60°C. After 30 min the mixture was cooled to 0°C and hydrolyzed by dropwise addition of 3 g of water. During this hydrolysis a gas release was observed ; when it ceased the cooling bath was removed and stirring was continued for 15 min. Vacuum filtration through a Na_2SO_4 pad, washing of the solid residue with hexane, drying (Na_2SO_4) and evaporation gave the crude silylenol ether which was used in the next step without further purification.

3-Trimethylsiloxy-2 cyclopentene carbonitrile 3a

^1H NMR (CCl_4) δ 0.25 (s, 9H), 2.10 - 2.60 (m, 4H), 3.30 - 3.65 (m, 1H), 4.50 (m, 1H) ; IR (CCl_4) 2200, 1640 cm^{-1}.

3-Trimethylsiloxy-2 cyclohexene carbonitrile 3b

^1H NMR (CCl_4) δ 0.10 (s, 9H), 1.60 - 2.10 (m, 6H), 3.13 (m, 1H), 4.64 (br d, J = 4 Hz, 1 H); IR (CCl_4) 2240, 1660 cm^{-1} (in agreement with results of ref. 11).

3-Trimethylsiloxy-2 cycloheptene carbonitrile 3c

^1H NMR (CCl_4) δ 0.19 (s, 9H), 1.45 - 2.50 (m, 8H), 3.08 - 3.45 (m, 1H), 4.87 (d, J = 7.5 Hz, 1H).

1-Methyl 3-trimethylsiloxy 2-cyclopentene carbonitrile 3d

^1H NMR (CCl_4) δ 0.26 (s, 9H), 1.43 (s, 3H), 1.68 - 2.54 (m, 4H), 4.59 (m, 1H) ; IR (CCl_4) 2230, 1640 cm^{-1}.

3-Oxo 2-phenylthiomethylcyclopentane carbonitrile 4a

A mixture of the crude silylenol ether 3a prepared from 20 mmol of cyclopentenone, 20 mL of dry CH_2Cl_2, 1.90 g (12 mmol) of chloromethylphenyl sulfide 12, 240 mg (1.07 mmol) of dry $ZnBr_2$ was stirred at room temperature for 18h. Evaporation gave a residue from which 1.62 g (35% from 2a) of phenylthiomethyl cyclopentane carbonitrile 4a was isolated by column chromatography on 140 g of silica gel (hexane-ether, 40:60). ^1H NMR (CCl_4) δ 1.90 - 3.65 (m, 8H), 7.00 - 7.40 (m, 5H) ; IR (CCl_4) 2230, 1760, 1590 cm^{-1} ; MS, m/e (relative intensity) 231 (M^+, 1.5), 121 (43), 110 (100), 109 (26), 66 (89), 39 (29) ; Anal. calcd for $C_{13}H_{13}NOS$: C, 67.50 ; H, 5.66 ; N, 6.06 ; S, 13.86. Found : C, 67.70 ; H, 5.75 ; N, 6.27 ; S, 13.63.

3-Oxo 2-phenylthiomethyl cyclohexane carbonitrile 4b

The procedure was the same as described above for 4a except that 3.17 g (20 mmol) of chloromethylphenyl sulfide (instead of 12 mmol) was used. Evaporation gave a residue from which 2.27g (46% from 2b) of phenylthiomethyl cyclohexane carbonitrile 4b was isolated by column chromatography on 170 g of silica gel (hexane-ether, 40:60). ^1H NMR (CCl_4) δ 1.60 - 4.25 (m, 10H), 7.05 - 7.50 (m, 5H); IR (CCl_4) 2240, 1728 cm^{-1} ; MS, m/e (relative intensity) 245 (M^+, 2), 135 (36), 110 (100), 107 (70), 79 (30), 66 (40), 39 (32) ; HRMS, m/e 245.0918 (calcd for M^+, $C_{14}H_{15}NOS$: 245.0874).

3-Oxo 2-phenylthiomethyl cycloheptane carbonitrile 4c

The procedure was the same as described above for 4a except that 3.17 g (20 mmol) of chloromethylphenyl sulfide (instead of 12 mmol) was used. Evaporation gave a residue from which 1.97g (38% from 2c) of phenylthiomethyl cycloheptane carbonitrile 4c was isolated by column chromatography on 180 g of silica gel (hexane-ether, 85:15 then 65:35). ^1H NMR (CCl_4) δ 1.50 - 3.75 (m, 12 H), 7.20 - 7.40 (m, 5H) ; IR (CCl_4) 2240, 1715, 1585 cm^{-1} ; MS, m/e (relative intensity) 259 (M^+, 24), 110 (100), 109 (36), 68 (30), 66 (60), 65 (41), 55 (56), 41 (36), 39 (52) ; HRMS, m/e 259.1060 (calcd for M^+, $C_{15}H_{17}OSN$ 259.1031).

1-Methyl 3-oxo 2-phenylthiomethyl cyclopentane carbonitrile 4d

The procedure was the same as described above for 4a except that 2.06 g (13 mmol) of chloromethylphenyl sulfide (instead of 12 mmol) was used. Evaporation gave a residue from which 1.03g (21% from 2d) of 1-methyl 3-oxo 2-phenylthiomethyl cyclopentane carbonitrile 4d was isolated by column chromatography on 140 g of silica gel (hexane-ether, 40:60). For analytical and spectral data see below.

Preparation of the same product 4d using $TiCl_4$

To a stirred solution of 1.51 g ($\simeq$ 7.74 mmol) of the crude silylenol ether 3d (prepared from 0.897 g (9.34 mmol) of 3-methyl cyclopentenone) and 1.73 g (10.9 mmol) of chloromethylphenyl sulfide in 12 ml of dry CH_2Cl_2 at -25°C under nitrogen, 3.4 mL of a solution of $TiCl_4$ 2.54 M in CH_2Cl_2 (8.64 mmol) was added dropwise. After one hour stirring, the reaction mixture was poured into 40 ml of saturated $NaHCO_3$ aqueous solution. After filtration and washing of the solid with ether, extraction of the aqueous phase with ether (3x15 ml), drying of the ether phase (Na_2SO_4) and evaporation, the crude product was obtained. Column chromatography on 65 g of silica gel (hexane-ether, 40:60) gave 0.572 g (25% from 2d) of 1-methyl 3-oxo 2-phenylthiomethyl cyclopentane carbonitrile 4d. ^1H NMR (CCl_4) (for mixture of both stereoisomers in 1:4 ratio) δ 1.30 (s, 0.6 H), 1.63 (s, 2.4 H), 1.90 - 3.00 (m, 7H), 7.14 (m, 5H) ; ^{13}C NMR ($CDCl_3$) (predominant isomer) 25.4, 31.2, 34.1, 35.7, 42.1, 57.4, 120.8 to 134.9 (7C), 212.6 ; off resonance ^{13}C NMR spectrum of mixture of both stereoisomers ($CDCl_3$) showed two quadruplets : 18.7 and 25.4, C of CH_3 in 1:4 intensity ratio. As the less sterically crowded carbon should appear at lower field, predominant isomer is probably trans-(1-methyl 2-phenylthiomethyl) 3-oxo cyclopentane carbonitrile; IR (CCl_4) (for mixture of both stereoisomers) 2230, 1760 cm^{-1} ; MS (for mixture of both stereoisomers), m/e (relative intensity) 245 (M^+, 1.3), 120 (36), 110 (100), 79 (61), 66 (37), 52 (29), 39 (29) ; Anal. calcd for $C_{14}H_{15}NOS$: C, 68.54 ; H, 6.16 ; N, 5.71 ; S, 13.07. Found (for mixture of both stereoisomers) C, 68.76 ; H, 6.16 ; N, 5.48 ; S, 12.86.

1-Methyl 3-oxo cyclopentane carbonitrile 7

The two preceding experiments gave compound 7 beside 4d. 7 which was eluted after 4d by column chromatography showed the following spectral features : IH NMR (CCl4) δ 1.53 (s, 3H), 1.96 - 2.90 (m, 6H) ; IR (CCl4) 2220, 1760 cm-1 ; MS, m/e (relative intensity) 123 (M^+, 28), 94 (32), 67 (100), 55 (67), 41 (40), 39 (25).

3-Dimethyltertiobutylsiloxy 1-methyl 2-cyclopentene carbonitrile 8 and its alkylation by chloromethylphenyl sulfide

Conjugate addition of cyanodimethyltertiobutyl silane [13] to 3-methyl cyclopentenone by the same procedure as for cyanotrimethyl silane gave the crude silylenol ether 8. IH NMR (CCl4) δ 0.22 (s, 6H), 0.95 (s, 9H), 1.45 (s, 3H), 1.74 - 2.65 (m, 4H), 4.60 (br s, 1 H) ; IR (CCl4) 2230, 1640 cm-1.

Its alkylation by chloromethylphenyl sulfide in the presence of TiCl4 by the same procedure as for 3a gave a mixture of 7 and 4d (both stereoisomers). Intensity ratio for IH NMR methyl groups signals (1.30, 1.53, 1.63) was the same as for experiments via cyanotrimethyl silane.

2-Methylene 3-oxo cyclopentane carbonitrile 6a

To a stirred solution of 0.540 g (2.34 mmol) of 3-oxo 2-phenylthiomethyl cyclopentane carbonitrile 4a in 10 mL of MeOH 2.16 g (7.03 mmol of KHSO5) of oxone dissolved in 10 mL of water was added dropwise (20 min) at room temperature. After 4 h, the reaction mixture was extracted with CH2Cl2 (3x25 mL). The organic phase was dried (Na2SO4) and evaporated to give the crude 3-oxo 2-phenylsulfonylmethyl cyclopentane carbonitrile 5a. IH NMR (CDCl3) δ 1.90 - 3.90 (m, 8H), 7.10 - 8.10 (m, 5H) ; IR ($CDCl_3$) 2250, 1760, 1590, 1310, 1150 cm-1.

5.5 g of basic alumina Fluka 5016 A, activity I, was added (5 min) to a stirred solution of the crude 5a in 50 mL of CH2Cl2. After an additional stirring of 20 min, alumina was removed by vacuum filtration and washed with CH2Cl2. Evaporation of the solvent gave the crude 2-methylene 3-oxo cyclopentane carbonitrile 6a which was purified by flash column chromatography on 16 g of silica gel (pentane-ether, 80:20). Thus, 0.153 g (54% from 4a) of 2-methylene 3-oxo cyclopentane carbonitrile 6a were obtained. IH NMR (CDCl3) δ 2.00 - 2.70 (m, 4H), 3.63 - 3.92 (m, 1H), 5.77 (d, J = 3 Hz, 1H), 6.18 (d, J = 3 Hz, IH). When 3.63 - 3.92 signal was irradiated singlets instead of doublets were observed for 5.77 and 6.18 signals ; IR (CCl4) 2200, 1740, 1650 cm-1 ; UV (H2O) λmax (ϵ) 226 nm (6600), 322 nm (26) ; MS, m/e (relative intensity) 121 (M^+, 50), 93 (57), 66 (59), 65 (100), 39 (24), 38 (24) ; HRMS, m/e 121.0545 (calcd for M^+, C_7H_7NO 121.0528). IH NMR and IR spectra are approximatively in agreement with results of Marx and Minaskanian Ic, however these authors don't mention the signal at 3.63 - 3.92 ppm.

2-Methylene 3-oxo cyclohexane carbonitrile 6b

Oxidation of 0.503 g (2.05 mmol) of 2-phenylthiomethyl cyclohexane carbonitrile 4b by the same procedure as for 4a gave the crude 3-oxo 2-phenylsulfonylmethyl cyclohexane carbonitrile 5b. IH NMR (CDCl3) δ 1.50 - 4.30 (m, 10 H), 6.90 - 7.75 (m, 5H) ; IR (CDCl3) 2245, 1730, 1605 cm-1. Treatment of the crude 5b with basic alumina by the same procedure as for 5a gave the crude 2-methylene 3-oxo cyclohexane carbonitrile 6b, a very sensitive compound, which could not be purified. The mass of 6b (evaluated by NMR) was 55.3 mg (20% from 4b). IH NMR (CCl4) several signals including δ 5.67 (d, J = 2 Hz, 1H) ; 6.17 (d, J = 2 Hz, IH) ; IR (CCl4) 2250, 1710, 1625 cm-1 ; MS, m/e (relative intensity) 135 (M^+, 66), 107 (97), 106 (64), 92 (75), 80 (60), 79 (74), 41 (100), 39 (76) ; HRMS, m/e 135.0710 (calcd for M^+, C_8H_9NO 135.0684).

2-Methylene 3-oxo cycloheptane carbonitrile 6c

Oxidation of 0.590 g (2.28 mmol) of 3-oxo 2-phenylthiomethyl cycloheptane carbonitrile 4c by the same procedure as for 4a gave the crude 3-oxo 2-phenylsulfonylmethyl 2-cycloheptane carbonitrile 5c. IH NMR (CDCl3) δ 1.70 - 4.00 (m, 12H), 7.70 - 8.20 (m, 5H). Treatment of the crude 5c with basic alumina followed by purification, by the same procedure as for 5a, gave 0.153 g (45% from 4c) of 2-methylene 3-oxo cycloheptane carbonitrile 6c. IH NMR (CDCl3) δ 1.60 - 2.35 (m, 6H), 2.81 (m, 2H), 3.81 (m, IH), 5.79 (s, IH), 6.33 (s, IH) ; IR (CCl4) 2242, 1705, 1615 cm-1 ; UV (H2O) λmax (ϵ) 224 nm (4000), 310 nm (50) ; MS, m/e (relative intensity) 149 (M^+, 15), 68 (44), 55 (100), 54 (70), 41 (72), 39 62), 38 (44) ; HRMS, m/e 149.0854 (calcd for M^+, $C_9H_{11}NO$ 149.0841).

1-Methyl 2-methylene 3-oxo cyclopentane carbonitrile 6d

Oxidation of 0.590 g (2.41 mmol) of 1-methyl 3-oxo 2-phenylthiomethyl cyclopentane carbonitrile 4d by the same procedure as for 4a gave the crude 1-methyl 3-oxo 2-phenylsulfonylmethyl cyclopentane carbonitrile 5d. IH NMR (CDCl3) (both stereoisomers)δ1.37 (s, 0.9 H), 1.80 s, 2.1 H), 2.00 - 3.90 (m, 7H), 7.40 - 8.05 (m, 5H) ; IR (CDCl3) 2235, 1760 cm-1. Treatment of the crude 5d with basic alumina followed by purification, by the same procedure as for 5a, gave 0.189 g (58% from 4d) of 1-methyl 2-methylene 3-oxo cyclopentane carbonitrile 6d. IH NMR (CCl4) δ1.56 (s, 3H), 1.80 - 2.60 (m, 4H), 5.56 (s, IH), 6.06 (s, IH) ; IR (CCl4) 2230, 1740, 1645 cm-1 ; MS, m/e (relative intensity) 135 (M^+, 57), 120 (89), 107 (34), 79 (100), 52 (57) ; HRMS, m/e 135.0683 (calcd for M^+, C_8H_9NO 135.0684).

3-Oxo 2-phenylsulfinylmethyl cyclopentane carbonitrile and attempts of its conversion into 2-methylene 3-oxo cyclopentane carbonitrile 6a

To a stirred solution of 0.183 g (0.79 mmol) of 3-oxo 2-phenylthiomethyl cyclopentene carbonitrile 4a in 20 mL of MeOH was added during 10 min at 0°C a solution of 0.184 g (0.86 mmol) of NaIO4 in 20 mL of H2O 7. After 17 h stirring at room temperature the reaction mixture was extracted with CH2Cl2 (3x15 mL), the organic phase was dried (Na2SO4) and solvents were evaporated to give the crude 3-oxo 2-phenylsulfinylmethyl cyclopentane (with a small amount of 2-methylene 3-oxo cyclopentane carbonitrile 6a). IH NMR (CDCl3) δ 1.90 - 4.37 (m, 8H), 7.15 - 8.10 (m, 5H) ; IR (CDCl3) 2240, 1760, 1045 cm-1. At the top of a column packed with 5 g of silica gel and hexane was introduced the crude preceding oil in 2 mL of CH2Cl2 7. Elution by 50 mL of AcOEt-hexane-CH2Cl2, 6:40:54 gave several fractions in which 2-methylene 3-oxo cyclopentane carbonitrile 6a was present (impure product; NMR yield 36%) ; its further purification by column chromatography on silica gel failed. In another experiment the crude sulfoxide was heated in refluxing CDCl3 ; IH NMR spectroscopy showed conversion

into 2-methylene 3-oxo cyclopentane carbonitrile 6a as checked by the presence of the 5.77 and 6.18 ppm signals, but this compound was not very stable at this temperature

3-Oxo 2-phenylthiomethyl cyclopentane carboxylic acid 9

1.073 g (4.65 mmol) of 3-oxo 2-phenylthiomethyl cyclopentane carbonitrile 4a, 0.58 g (9.3 mmol) of ethylene glycol, 35 mL of cyclohexane and 0.010 g (0.058 mmol) of p-toluenesulfonic acid were refluxed for 20 h in a Dean-Stark apparatus. After cooling and addition of 20 mL of ether, the organic phase was washed with 5% $NaHCO_3$ aqueous solution (10 mL) and with water (3X10 mL) and dried ($MgSO_4$). Evaporation gave 1.28 g of the crude 3,3-ethylenedioxy 2-phenylthiomethyl cyclopentane carbonitrile. IH NMR (CCl4) δ1.70 - 3.40 (m, 8H), 3.86 (br s, 4H), 7.01 - 7.48 (m, 5H) ; IR (CCl4) 2250, 1590, 1325, 1160 cm-1. The crude preceding acetal was stirred for 16 h at 120°C with ethylene glycol (10 mL), 84% KOH (1.03 g; 15.4 mmol of KOH) and water (0.285 g, 16 mmol). After cooling, addition of 20 mL of ether and stirring the aqueous phase was separated and acidified to pH 4 by slow addition of 1N HCl. This aqueous phase was extracted with ether (3x20 mL) and the organic phase was dried (Na_2SO_4). Evaporation gave 1.06 g of the crude 3,3-ethylenedioxy 2-phenylthiomethyl cyclopentane carboxylic acid. IH NMR (CCl4) δ1.70 - 3.50 (m, 8H), 3.84 (m, 4H), 7.10 - 7.55 (m, 5H), 11.80 (s, 1H) ; IR (CCl4) 3300, 2400, 1715, 1590, 1485 cm-1. The crude preceding acid was stirred for 24 h at room temperature with 10 mL of acetone and one drop of concentrated sulfuric acid. Evaporation and purification by column chromatography on 20 g of silica gel (hexane-CH_2Cl_2-AcOEt, 80:18:2 to 35:60:5) gave 0.790 g (68% from 4a) of 3-oxo 2-phenylthiomethyl cyclopentane carboxylic acid 9. IH NMR (CCl4) δ1.60 - 4.20 (m, 8H), 7.20 (m, 5H), 10.80 (s, 1H) ; IR (CCl4) 3450, 2450, 1757, 1715, 1590 cm-1 ; MS (chemical ionization, NH3), m/e (relative intensity) 268 (65), 251 (85), 250 (96) ($(M + NH_4)^+$-H_2O), 187 (27), 158 (25), 123 (50), 110 (100), 109 (39) ; Anal. calcd for $C_{13}H_{14}O_2S$: C, 62.38 ; H, 5.64 ; S, 12.81. Found : C, 62.13; H, 5.81 ; S, 12.92.

3-Oxo 2-phenylthiomethyl methyl cyclopentane carboxylate 10

A solution of 3.47 mmol of diazomethane in 80 mL of ether was added at room temperature to a solution of 0.790 g (3.16 mmol) of 3-oxo 2-phenylthiomethyl cyclopentane carboxylic acid 9 in 80 mL of ether-CH_2Cl_2, 50:50. After 1 h the solvents were evaporated and 0.834 g (3.16 mmol) (100%) of the pure 3-oxo 2-phenylthiomethyl methyl cyclopentane carboxylate 10 were obtained. IH NMR (CCl4) δ1.70 - 3.30 (m, 8H), 3.60 (s, 3H), 7.15 (m, 5H) ; IR (CDCl3) 1740, 1445 cm-1 ; MS, m/e (relative intensitiy) 264 (M^+, 33), 110 (100), 109 (36), 95 (44), 85 (65), 67 (54), 66 (32), 65 (32), 59 (31).

2-Methylene 3-oxo methyl cyclopentane carboxylate 12

The oxidation of 0.530 g (2.01 mmol) of 3-oxo 2-phenylthiomethyl methyl cyclopentane carboxylate 10 by the same procedure as for 4a gave the crude 3-oxo 2-phenylsulfonylmethyl methyl cyclopentane carboxylate 11. IH NMR (CDCl3) δ1.95 - 4.05 (m, 8H), 3.79 (s, 3H), 7.55 - 8.15 (m, 5H); IR (CDCl3) 1745, 1310 cm-1. Treatment of the crude 11 with basic alumina followed by purification, by the same procedure as for 4a gave 0.161 g (52% from 10) of 2-methylene 3-oxo methyl cyclopentane carboxylate 12. Spectral data (in agreement with litt. [a,e,j]) : IH NMR (CCl4) δ1.95 - 2.60 (m, 4H), 3.55 - 3.90 (m, 1H), 3.70 (s, 3H), 5.50 (dd, J1 = 2.3 Hz, J2 = 1 Hz, 1H), 6.04 (dd, J1 = 2.3 Hz, J2 = 1 Hz, 1H); IR (CCl4) 1740, 1640, 1170 cm-1 ; UV (H_2O) λmax (ϵ) 232 nm (6400), 320 nm (41) ; MS, m/e (relative intensity) 154 (M^+, 9), 126 (100), 98 (39), 95 (38), 67 (62), 59 (45), 44 (55), 41 (46), 39 (70) ; HRMS, m/e 154.0639 (calcd for M^+, $C_8H_{10}O_3$ 154.0630).

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